growth factor, neutrophil activating protein 2, platelet derived growth factor, stem cell factor, transforming growth factor, tumor necrosis factors and vascular endothial growth factor.

22. (Amended) The [viral complex] chimeric virus of claim 20 in which the antibody binds an antigen which is selected from the group consisting of class I MHC antigens, class II MHC antigens, internalizing cell-surface receptors and viral receptors.

23. (Amended) A [viral complex] chimeric virus which comprises a gene of interest under the control of an appropriate viral sequence and a chimeric alphavirus envelope protein.--

Please cancel claims 11-17, 24-26 and 32-47 without prejudice to applicants' ability to seek patent protection for that subject matter in a later-filed divisional or continuation application.

REMARKS

Claims 1- 47 were pending. Applicants have canceled claims 11-17, 24-26 and 32-47 without prejudice and amended claims 1-3, 6-9 and 18-23. Accordingly, claims 1-10, 18-23 and 27-31 are presently under examination.

The amendments to the claims raise no issue of new matter. Support for "high efficiency" may be found *inter alia* in the specification and on page 21, lines 26-27; page 25, lines 2-4. Support for "sufficient to bind an Fc domain of an antibody with strong affinity" may be found *inter alia* in the specification and on page 8, lines 23-27; page 12, lines 3-6;

page 15, lines 28-30; page 20, lines 23-24; page 21, lines 17-19. Support for "chimeric virus" may be found *inter alia* in the specification and on page 4, lines 11-14; page 9, lines 15-17; page 17, lines 34-35; page 19, lines 11-12 and 37-38; page 20, 31-33; page 21, 24-26, etc. Accordingly, Applicants respectfully request that the Examiner enter this amendment.

On page 3 of the Office Action, the Examiner objected to the specification for a variety of informalities. In response, Applicants have amended the specification to correct the informalities.

The rejection of claims 1-10, 18-23 and 27-31 under 35 U.S.C. § 112, first paragraph should be withdrawn

On page 3 of the Office Action, the Examiner stated:

Claims 1-10, 18-23 and 27-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the insertion of the particular "ZZ" IgG binding domain of Protein A into a viral vector, does not reasonably provide enablement for insertion of a portion of that domain, or for a portion of any IgG binding domain of Protein A. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to viral vectors having at least a portion of an IgG binding domain of Protein A.

The specification sets forth the use of the specific, synthetic ZZ domain, which is an IgG binding domain of Protein A from Staphylococcus aureus. The entire domain is inserted into he viral envelope. The specification does not disclose what portions of the ZZ domain are necessary and sufficient to retain IgG binding properties, nor does this information appear to be available in the art such that one of skill in the art would be able to identify portions of the ZZ domain which would function as set forth in the specification and claims.

Protein: protein interactions are not strictly predictable such that one can look at the sequences of two proteins and immediately grasp what portions are necessary and sufficient for their interaction. While the skill in the art of virology and protein interactions is high, the identification of portions of polypeptides which would possess the desired properties is unpredictable. The specification does not provide working examples of any fragments or portions of the ZZ domain which would be useful in the invention. While working examples are not required in an application, the specification must provide adequate teachings and guidance such that one of skill in the art would be able to practice the invention.

Additionally, the specification does not disclose that any other IgG binding domain, or portion of any other IgG binding domain of Protein A would be useable in the invention. Protein A is known to have at least 4 IgG binding domains, having varying specificity for immunoglobulin. (see Surolia 1982 Trends Biochem. Sci 7:74-76). Consequently, it would not be clear to one of skill in the art whether any natural IgG binding domain, or portion thereof, would be able to function in the same manner as the synthetic ZZ binding domain disclosed in the specification.

As such, the specification is not enabling for the breadth of the claims.

Claims 1-10, 18-23, and 27-31 are rejected under 34 U.S.C. 112, first paragraph, because the specification, while being enabling for the insertion of synthetic Protein A IgG "ZZ" binding domain into a full length viral protein, does not reasonably provide enablement for fragments of those viral proteins. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims recite that the IgG binding domain of Protein A is fused with, or is inserted into the envelope protein or fragment thereof, and that the envelope protein or fragment is capable of directing particle assembly.

The specification, as filed, sets forth the insertion of the ZZ domain of Protein A into the full length envelope protein of Sindbis virus and the replacement of particular sequences in the Mo-MuLV envelope protein with the ZZ domain. The specification does not disclosure the use of fragments of the Sindbus virus envelope gene, nor does it describe any other fragments of the Mo-MuLV envelope gene. Applicant does not disclose which portions of those genes are necessary and sufficient to direct particle assembly. The term "fragment" can encompass peptides as small as one amino acid, but such fragments are not described in the specification. Applicant fails to identify the regions of the viral envelope genes necessary to direct particle assembly, nor is it clear that one of skill in the art would readily be able to identify such regions. Applicant provides no guidance as to how one of skill in the art could identify such fragments of the viral envelope proteins that could direct particle assembly. While working examples are not required in the specification, the specification must provide appropriate teachings and guidance such that one of skill in the art could practice the invention as claimed.

In response, without conceding the correctness of the Examiner's position and to expedite the prosecution of the claimed subject matter, applicants have deleted the language "a portion of" from claims 1 and 18 and their dependent claims. In order to more clearly define the claims, they have been amended to recite "an IgG-binding domain of protein A sufficient to bind an Fc domain of an antibody with strong affinity." Applicants maintain that the specification is fully enabling for the scope of the claims as amended. Both the IgG binding domain of protein A and viral envelop proteins are exemplified, though the claims are not limited to Applicants's examples.

On pages 16 and 17 the specification discloses immunoblot and ELISA assays to determine whether in fact the IgG binding domain protein A is sufficient to react with antibodies. As can be seen in Figure 2B, the IgG binding activity occurs in a concentration dependent manner. One of ordinary skill could readily determine if an IgG binding domain protein A was sufficient to bind with strong affinity. Given that the necessary assays are exemplified on pages 16 and 17, the specification is fully enabling such that one of ordinary skill could practice the invention.

Regarding the Examiner's rejection of the claim language "or fragment thereof," without conceding the correctness of the Examiner's position and to expedite the prosecution of the claimed subject matter, applicants have deleted that language from claim 1.

The rejection of claims 3-5, 9 and 18-23 under 35 U.S.C. § 112, second paragraph should be withdrawn

On page 6 of the Office Action the Examiner stated:

> Claims 3-5, 9, and 18-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
>
> Claim 3 is rendered vague and indefinite by the use of the phrase "the vector further comprises a portion of the gp70." It is unclear what Applicant is claiming. Is this gp70 in addition to the viral envelope protein recited in claims 1 and 2? Or is the viral envelope protein recited in the independent claim intended to by the gp70? It would appear from claims 4 and 5 that Applicant intends the latter, but the claim, as written, is not so limited.
>
> Claim 9 recites the limitation "the chimeric gene" in reference to claim 8. There is insufficient antecedent basis for this limitation in the claim. Neither claim 8, nor the claims from which it depends, recites "a chimeric gene".
>
> Claims 18-23 are rendered vague and indefinite by the use of the term "viral complex". The claims do not recite a virus such that a viral complex can result. The claim merely recites a protein and a gene of interest. These components do not form viral complexes.

In response, without conceding the correctness of the Examiner's position, Applicants have amended the claims to address the § 112, second paragraph rejections.

Given the claim amendments, none of which were made to overcome art rejections, Applicants believe that the Examiner's rejections under 35 U.S.C. § 112 have been addressed Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 112 be withdrawn.

The rejection of claims 3-5, 9 and 18-23 under 35 U.S.C. § 103 should be withdrawn given that neither Barber, Wickham or Nilsson alone or in combination hint or suggest transducing a cell with high efficiency

On page 7 of the Office Action, the Examiner stated:

Claims 1-10, 18-23, and 27-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barber *et al.* (US Patent 5,591,624) and Wickham *et al.* (US Patent 5,846,782), in view of Nilsson *et al.* (Nilsson *et al.* 1987 Protein Eng. 1: 107-113).

Claims 1-10 are drawn to viral vectors having an IgG binding domain fused with, or inserted into a viral envelope gene. Gp70 of Mo-MuLV and E2 of Sindbis are preferred envelope genes. Claims 18-23 are drawn to viral complexes comprising the chimeric envelope protein and a gene of interest. Claims 27-31 are drawn to packaging cell lines comprising the vectors, and heterologous genes of interest.

Barber *et al.* disclose that viral surface proteins can be altered to redirect their specificity. At column 20, lines 64-65, Barber *et al.* specifically disclose that the envelope protein of retroviruses (particularly the gp70 of Mo-MuLV) can be modified to comprise a sequence which would bind to the Fc portion of an antibody. The synthetic ZZ IgG binding domain sequences of Protein A disclosed by Nilsson *et al.* is such a binding sequence. This modification of the envelope genes is done to alter the viral tropism and to facilitate infection of particular cell types, which then mediates gene transfer. Monoclonal antibodies are bound to the IgG binding domain on the viral surface, then the viral complex can be used to infect cell types which react with the particularly selected monoclonal antibody. The virus can carry genes encoding various heterologous sequences, such as drug resistance or sensitivity genes, or genes encoding cell cycle proteins.

Wickham *et al.* disclose various viral vectors which have modified surface proteins such that particular cell types can be targeted. Wickham *et al.* identifies suitable viral vectors, including retroviruses, and alphaviruses (see column 12). Both Sindbis and Mo-MuLV are specifically recited as desirable vectors. Wickham discloses a list of heterologous genes of interest which may be part of a viral complex (see column 14, line 37 to column 15, line 10).

Taken together, the instant invention appears to be the same or slightly different from the prior art of altering viral vector tropism through modification of the envelope sequence.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the use of the IgG binding domain of Protein A, as it binds to monoclonal antibodies. Barber *et al.* disclosed that being able to bind particular monoclonal antibodies to an Fc binding region on a viral complex would provide directed targeting for gene transfer. Both Barber *et al.* and Wickham *et al.* disclose viral vectors suitable for such modifications, as well as heterologous genes for gene transfer. Nilsson *et al.* provide the synthetic IgG binding domain. Based on the aforementioned disclosures it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In response, Applicants respectfully traverse the rejection. While many have suggested the desirability of altering the tropism of viruses for targeting and gene therapy, the literature is full of failure and false promises. Merely by way of example, Applicants point to the publications described below. Copies may be found in the attached Information Disclosure Statement. For example, retroviruses encoding an Fv antibody chain at the N terminus of the MLV *env* gene have been able to recognize epitopes but the transfection rate is very poor. See, Goud *et al.* (1988), Ager *et al.* (1998). Kasahara prepared a chimeric ecotropic virus with an erythropoietin envelop fusion protein. It was able to infect human cells. Kasahara *et al.* (1994). But the transfection rate is very poor. Kabat *et al.* (1995).

While the examiner's cited references, Wickham and Barber, suggest the desirability of altering viral tropism are merely examples' invitations to try. As described above, the literature is full of examples of such suggestions, but they have resulted in very low rates of transfection.

Regarding the Wickham reference, what Applicants have surprisingly discovered is viral vectors and chimeric viruses capable of transducing a target cell with high efficiency. In fact, Wickham himself conceded this fact when some of the work corresponding to Applicants' claimed invention published. For Applicants' own work, see Ohno *et al.* (1997). Specifically, Wickham (1997) describes in a research news article that one of the "principal problems encountered in targeting gene delivery [has] been loss of the viral vectors' original transduction efficiency." "Groups trying to target retrovirus have been hampered by the often dramatic reductions of transduction efficiency." He states that "ablation of native adenovirus receptor binding, as well as the ease of synthesizing exogenous targeting moieties have been somewhat problematic." He concedes that the "approach successfully used for Sindbis virus largely avoids the difficulties above." Wickham (1997). Accordingly, even the first named author of the Examiner's primary reference published a glowing report praising the benefits of Applicants' claimed invention. Contrary to the Examiner's assertion, Wickham can not provide one of ordinary skill with a reasonable expectation of success.

The Barber reference merely makes a passing reference to a possible alteration of the tropism of retroviruses. It provides no description of how to make the claimed invention that can transduce a target cell with high efficiency. Barber is based on a series of applications filed in 1988 - 1990. If Barber actually provided one of ordinary skill a reasonable expectation of success, Wickham would never have written his glowing article praising Applicants' invention.

Nilsson does nothing to remedy the fundamental shortcomings of Wickham and Barber. Nilsson merely discloses a synthetic IgG binding domain. There is no way that Nilsson alone, or in combination, hint or suggest, much less provide a reasonable expectation of success in making the claimed viral vectors or chimeric viruses for transducing a target cell with high efficiency. Moreover, there is no invitation to combine the disparate references.

Given the claim amendment and remarks above, Applicants believe that the Examiner's rejections under 35 U.S.C. § 103 have been addressed. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103 be withdrawn.

CONCLUSIONS

Applicants believe that this response overcomes all of the rejections. Accordingly the claims are now in condition for allowance. If any issues remain in connection with this application, Applicants encourage the Examiner to call the undersigned at (800) 760-9090.

Respectfully submitted,

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